Bioassay, carcinogenesis and tissue culture

Committee:
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TOBACCO INDUSTRY RESEARCH COMMITTEE

150 East Forth-second Street New York, New York

Application For Research Grant

October 25, 1960

1. Name of Investigator: William S. Murray, Sc.D.

2. Title: Senior Staff Scientist

3. Institution & Address: Roscoe B. Jackson Memorial Laboratory
Bar Harbor, Maine

4. Project or Subject: Studies on Physiology of Mice of Different Ages.

The long-term goal is to contribute to our knowledge of various factors influencing tissue reactions and changes, including neoplasia, by a more extensive use of old mice than has hitherto been made. The immediate aims and plans of procedure are listed (in section 5) under six headings.

5. Detailed Plan of Procedure:

(1) Do old mice exert the same type and degree of modifying influence on transplants of tissues as do young adults?

Transplants of tumor and of normal tissue into successive transplant generations of old mice will be made under conditions similar to those described by Barrett, Hauschka, and others. The tolerance of these "modified" tissues will be studied by periodic reinoculation into the "negative" parental strain (the parental strain in which the tumor did not originate).

(2) How do old animals react to various doses of, and types of exposure to, the M.T.I. (mammary tumor inciter)? What are the influences on morbidity and mortality of various strains injected with filtrates, or receiving transplants, of various tissues and organs (with or without M.T.I.) from the same and from alien strains?

Injections of blood, and of filtrates of tissue, and transplantation of various tissues containing the M.T.I. will be made into old animals of the same

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and of alien strains. The systemic and local effects will be observed physiologically and histologically. Parallel experiments with blood, filtrates, and transplants free from M.T.I. will be conducted and the results will be compared.

(3) What is the type, rate, and sequence of spread of the M.T.I. when it is introduced locally and at various sites and ages?

Neonatal, young adult, and old mice with the M.T.I. will provide the specific tissues to be transferred to animals without the M.T.I. but susceptible to it. Specific tissues will be removed at intervals from the host animals to see whether or not they contain, and can transmit, the M.T.I.

(4) Can characteristic different degrees of activity of the M.T.I. be produced by substrains of hybrids derived from crosses into which the M.T.I. is introduced by a single animal? If so, are these differences the result of change in the agent, or of the genetic constitution of the substrains.

This is a long-term experiment, involving the establishment, and expansion to large numbers, of inbred strains of hybrids derived from a single-animal introduction of the M.T.I. In each generation, the effectiveness of the M.T.I. will be tested and compared by challenging animals without the M.T.I. but susceptible to it.

(5) Can the presence of the M.T.I. be detected by its use in combination with, or in sequence to, exposure to known carcinogens? Can these or other techniques hasten its detection, either directly, or by its influence on chemical carcinogenesis?

Agents known to influence the incidence of skin, lung, lymphatic, or leukemic neoplasia will be used in combination and in pre and post application to local and systemic injection of the M.T.I. The effects on neoplasia and on the physiology and histology of various tissues and organs will be observed and compared.

(6) Will gonadectomy, or other hormonal imbalances, induced after the reproductive period, influence the morbidity or mortality of inbred strains and their hybrids?

Operative techniques and injection will be used to produce hormonal imbalance in old animals beyond the reproductive period. They will be compared with controls receiving similar experimental challenges without hormonal modification. Populations of each sex will be separately studied.

6. Budget Plan:

Salaries	$ 8,219.00
Expendable Supplies	1,709.00
Permanent Equipment	1,390.00
Overhead (15%)	1,990.00
Other	1,950.00
Total	$15,258.00

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7. Anticipated Duration of Work:

Three years. This request, however, is in support of the project prior to May 1, 1961 (see section 10).

8. Facilities and Staff Available:

Adequate animal room, laboratory, and office space are available. Cleaning and caretaking facilities are established. The scientific personnel will consist of the applicant in cooperation with Dr. Clarence C. Little and two laboratory assistants (not yet selected). The necessary animals are available in a great variety of inbred strains (and their hybrids) and in large numbers.

9. Additional Requirements:

These consist of modest alterations to the animal room and the installation of benches in the laboratory space. These are included in the "other" item of the budget. The equipment item in the budget includes appropriation for freeze-drying apparatus and animal room equipment.

10. Additional Information:

This project, as outline above, duplicates a request being submitted to the National Institutes of Health for support during the period May 1, 1961 - April 30, 1964. The present proposal, in support of getting the project underway, is for the period December 1, 1960 - April 30, 1961.

In essence this represents the attempt of the writer to re-enter the experimental field, in cooperation with Dr. Clarence C. Little, to take advantage of the availability of unusual animal material to supplement knowledge in a segment of the biological field which has been largely neglected.

/s/ William S. Murray, Sc.D.
Director of Project

/s/ Dale J. Foley
Business Officer of the Institution

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